CARDIOVASCULAR MEDICINE

Does lung diffusion impairment affect exercise capacity in patients with heart failure?

P G Agostoni, M Bussotti, P Palermo, M Guazzi

See end of article for authors' affiliations

Correspondence to:
Dr Pier Giuseppe Agostoni, Centro Cardiologico Monzino, Institute of Cardiology, University of Milan, via Parea 4, 20138 Milan, Italy;
piergiuseppe.agostoni@cardiologicomonzino.it

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Objective: To determine whether there is a relation between impairment of lung diffusion and reduced exercise capacity in chronic heart failure.
Design: 40 patients with heart failure in stable clinical condition and 40 controls participated in the study. All subjects underwent standard pulmonary function tests plus measurements of resting lung diffusion (carbon monoxide transfer, T_{LCO}), pulmonary capillary volume (V_C), and membrane resistance (D_M), and maximal cardiopulmonary exercise testing. In 20 patients and controls, the following investigations were also done: (1) resting and constant work rate T_{LCO}; (2) maximal cardiopulmonary exercise testing with inspiratory O_2 fractions of 0.21 and 0.16; and (3) rest and peak exercise blood gases. The other subjects underwent T_{LCO}, D_M, and V_C measurements during constant work rate exercise.
Results: In normoxia, exercise induced reductions of haemoglobin O_2 saturation never occurred. With hypoxia, peak exercise uptake (peak $\dot{V}O_2$) decreased from (mean (SD)) 1285 (395) to 1081 (396) ml/min ($p < 0.01$) in patients, and from 1861 (563) to 1771 (457) ml/min ($p < 0.05$) in controls. Resting T_{LCO} correlated with peak $\dot{V}O_2$ in heart failure (normoxia < hypoxia). In heart failure patients and normal subjects, T_{LCO} and peak $\dot{V}O_2$ correlated with O_2 arterial content at rest and during peak exercise in both normoxia and hypoxia. T_{LCO}, V_C, and D_M increased during exercise. The increase in T_{LCO} was greater in patients who had a smaller reduction of exercise capacity with hypoxia. Alveolar–arterial O_2 gradient at peak correlated with exercise capacity in heart failure during normoxia and, to a greater extent, during hypoxia.
Conclusions: Lung diffusion impairment is related to exercise capacity in heart failure.

S everal lines of evidence suggest that gas diffusion across the alveolar–capillary membrane influences exercise capacity in patients with heart failure: first, lung transfer capacity for carbon monoxide (T_{LCO}) correlates with exercise capacity[1–3]; second, improvement in clinical symptoms and exercise capacity with angiotensin converting enzyme (ACE) inhibitors is correlated with an increase in T_{LCO}[4 5]; third, oxygen uptake kinetics can be altered by manipulation of lung diffusion[6]; and fourth, exercise performance can be improved in patients with heart failure by increasing the partial pressure of oxygen physiologically—that is, by exercising patients below sea level[7]—or artificially, by increasing the inspired oxygen fraction[8] or by positive pressure ventilation.[9] However, the physiological relation between reduction in exercise capacity and T_{LCO} impairment in heart failure is uncertain. This is because in heart failure, neither an exercise induced reduction in arterial oxygen content (Cao_2), nor the more easily measured exercise induced desaturation of haemoglobin—which is considered the clinical hallmark of T_{LCO} impairment—is commonly observed.[10] Nonetheless the role of Cao_2 in regulating the amount of oxygen available for the muscles, the so called oxygen delivery, during exercise is pivotal in heart failure. Indeed, oxygen delivery depends on Cao_2 and cardiac output, but in heart failure the increase in cardiac output during exercise is blunted. Several physiological factors regulate Cao_2 including the following: the systemic arterial Po_2 (Pao_2), which depends on alveolar Po_2, the gas exchange surface area, and the alveolar–arterial oxygen pressure gradient ($\Delta P[A–ao_2]$); the haemoglobin concentration; and the shape of the haemoglobin dissociation curve for oxygen. All these factors undergo exercise induced changes.[11] Gas exchange surface and $\Delta P[A–ao_2]$ are reflected by T_{LCO}.[12]

To evaluate the relation between lung diffusion impairment and exercise intolerance in chronic heart failure we studied in the correlations between T_{LCO}, Cao_2, and exercise capacity during normoxic and hypoxic conditions both at rest and during exercise. Different levels of inspired oxygen fraction (Fio_2) were chosen because during hypoxia, both Pao_2 and haemoglobin saturation with oxygen (Sao_2) are in the linear portion of the S shaped haemoglobin dissociation curve for oxygen, making it easier to study and understand the role of T_{LCO} in regulating Cao_2 and exercise capacity.

METHODS
Patient population
Forty patients with stable heart failure (mean (SD) age 61.9 (6.4) years; 30 male, 10 female) and 40 healthy controls (57.6 (9.6) years; 28 male, 12 female) participated in the study.

All the heart failure patients were in New York Heart Association (NYHA) functional class II or III and belonged to a cohort of heart failure patients regularly followed in our heart failure clinic. Heart failure aetiology was: ischaemic cardiomyopathy (15), idiopathic (11), alcoholic (7), HIV related (4), and related to antitumour drugs (3). Exclusion criteria included: a left ventricular ejection fraction > 35% by echocardiography, the presence of periodic breathing during exercise, primary pulmonary disease, unstable angina, recent myocardial infarction, and artificial pacemakers. Ten patients were active smokers, 20 were previous smokers (defined as patients who quit smoking more than five years ago), and 10

had never smoked. Treatment was stable and included: digitalis (13), diuretics (34), ACE inhibitors (29), angiotensin I blockers (8), β blockers (18), and amiodarone (18).

Healthy controls were chosen from patients' relatives and hospital employees or their friends. Eighteen were smokers, eight were previous smokers, and 14 never smoked. None was involved in regular exercise programmes.

The study was approved by the local ethics committee and all subjects provided their written informed consent.

Pulmonary function evaluation

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured in triplicate and calculated according to the American Thoracic Society criteria,[13] using a mass flow sensor (2200 Sensor Medics, Yorba Linda, California, USA). Maximum voluntary ventilation (MVV) was assumed to be either MVV measured in 12 seconds or $FEV_1 \times 40$, whichever was highest.[14] Predicted values are from Quanjer and colleagues, and Jones.[15][16] T_{LCO} was measured with the single breath constant expiratory flow technique. T_{LCO} data are reported as absolute values or as a percentage of predicted.[17] Molecular diffusion of carbon monoxide across the alveolar–capillary membrane (D_M) and pulmonary capillary blood volume (V_C) were measured according to the method of Roughton and Forster.[18] T_{LCO}, D_M, and V_C are linked by the following equation:

$$1/T_{LCO} = 1/D_M + 1/\theta V_C$$

where θ is the rate of reaction of carbon monoxide with haemoglobin and is inversely proportional to P_{O_2} in the alveolar air (PA_{O_2}). Therefore subjects inspired a gas mixture with 0.3% CH_4, 0.3% CO, and 0.3% C_2H_2 balanced with nitrogen with three different O_2 fractions equal to 20%, 40%, and 60%, respectively. This procedure allows measurement of T_{LCO} at different Pa_{O_2} values, thereby causing θ to vary and enabling calculation of D_M and V_C graphically.[18]

Cardiopulmonary exercise testing

Maximal cardiopulmonary exercise tests (V_{MAX} 29C, Sensor Medics) were done on a cycle ergometer (Ergometrics-800, Sensor Medics), using a personalised ramp protocol aimed at achieving peak exercise in around 10 minutes.[19] Data are reported as absolute values or as a percentage of the $\dot{V}_{O_2}$ max predicted.[14] Ventilation and partial pressures of inspiratory and expiratory gases were measured on a breath by breath basis. The anaerobic threshold was calculated by "V slope" analysis (plot of $\dot{V}_{CO_2}$ divided by $\dot{V}_{O_2}$) and oxygen pulse as $\dot{V}_{O_2}$/heart rate.

In subjects in group A (see below), a small brachial artery catheter was inserted to allow easy and repeatable arterial blood sampling. In these subjects two cardiopulmonary exercise tests were performed while they breathed a gas mixture with an Fi_{O_2} of 21% or 16% (equivalent to the oxygen tension found at an altitude of around 2000 m) in random order. Arterial blood was sampled in triplicate at rest, after at least 10 minutes of quiet breathing on the cycle ergometer, and again at peak exercise. These samples were used to measure haemoglobin concentrations, oxygen and carbon dioxide tensions, Ca_{O_2}, and pH (ABL 520, Radiometer, Copenhagen, Denmark). PA_{O_2} was determined from the equation:

$$PA_{O_2} = [(Bp \text{ (mm Hg)} - 47) \times Fi_{O_2} - Pa_{CO_2}/R]$$

where Bp = barometric pressure, Fi_{O_2} = oxygen inspired fraction, Pa_{CO_2} = arterial carbon dioxide partial pressure, and R = respiratory gas exchange ratio.

Study design

The first part of the protocol was the same for all subjects. Both patients and control subjects underwent standard pulmonary function tests, resting T_{LCO}, D_M, and V_C measurements (in the sitting position) and an incremental cardiopulmonary exercise test. At least one cardiopulmonary exercise test was performed before the formal study to familiarise the subjects with the techniques and procedures. Subjects were then randomly allocated into two groups, A and B, each comprising 20 heart failure patients and 20 normal controls.

Investigations in group A

In group A, T_{LCO} was also measured with the subjects sitting on the ergometer and after three and five minutes of light exercise (20% of the maximum workload achieved). The cardiopulmonary exercise tests, with an Fi_{O_2} of 21% and 16%, were done on the following days. The order of the two tests was randomised and a resting interval of more than six hours was allowed between each test.

Investigations in group B

In group B, only one cardiopulmonary exercise test was performed to assess exercise capacity while the subjects were breathing room air. T_{LCO}, D_M, and V_C were measured with the subjects sitting on the cycle ergometer and during light exercise (20% of maximum workload achieved) which lasted around five minutes.

Statistical analysis

Data are presented as mean (SD). Correlations were obtained by linear regression analysis and the best fit method. Differences were evaluated by analysis of variance (ANOVA) and the unpaired t test, applying the Bonferroni correction for multiple comparisons as appropriate. Multivariate stepwise regression model (SPSS 9.0) was used to identify independent predictors of T_{LCO} and peak exercise oxygen consumption (peak $\dot{V}_{O_2}$). All variables with a univariate probability value of $p < 0.05$ were included.

RESULTS

Pulmonary function and exercise capacity (all subjects)

Results of the pulmonary function tests were consistent with a mild restrictive defect in the heart failure patients (table 1). Compared with the normal controls, resting T_{LCO} was reduced in the heart failure group owing to a reduction in D_M with a normal V_C (table 1). $\dot{V}_{O_2}$ at peak exercise and at anaerobic threshold was 1285 (376)/800 (140) and 1866 (540)/1010 (290) ml/min in patients and controls, respectively ($p < 0.01$ for both conditions). Oxygen pulse at peak exercise was 10.0 (2.7) and 12.5 (3.5) ml/beat in patients and normal subjects, respectively ($p < 0.05$). In heart failure patients (fig 1, upper panel) but not in normal subjects (lower panel) resting T_{LCO} was significantly correlated with normoxic peak $\dot{V}_{O_2}$. To avoid

Table 1 Standard pulmonary function and lung diffusion tests in the whole study population

	Heart failure patients (n=40)	Normal controls (n=40)
FEV_1 (% pred)	86 (20)*	114 (21)
FVC (% pred)	74 (12)*	106 (12)
FEV_1 / FVC	115 (15)	108 (10)
MVV (% pred)	85 (20)	118 (17)
T_{LCO} (ml/min/mm Hg)	19.9 (5.5)*	28.0 (6.1)
T_{LCO} (% pred)	77 (19)*	108 (17)
D_M (ml/min/mm Hg)	29.0 (10.6)*	45.4 (12.8)
V_C (ml)	103.8 (40.8)	103.3 (38.2)

Data are presented as mean (SD).
*$p < 0.01$ v normal controls.
D_M, molecular diffusion for carbon monoxide across the alveolar capillary membrane; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MVV, maximum voluntary ventilation; pred, T_{LCO}, lung transfer capacity for carbon monoxide; V_C, capillary blood volume.
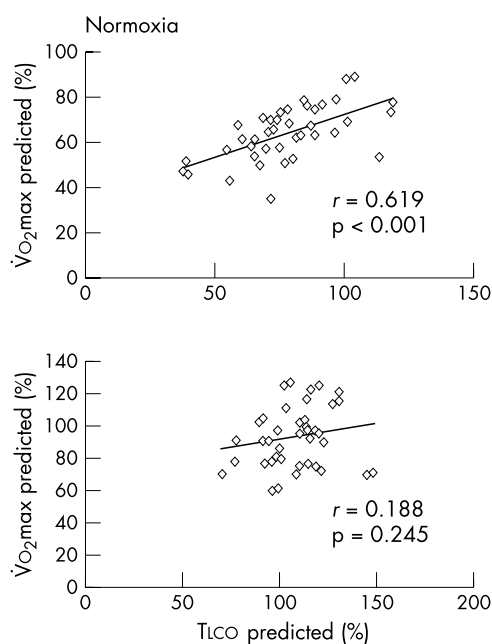
Figure 1 Peak $\dot{V}O_2$ during normoxia v resting lung transfer capacity for carbon monoxide (T_{LCO}) (reported as per cent of predicted) in heart failure patients (upper panel, n = 40) and healthy controls (lower panel, n = 40).
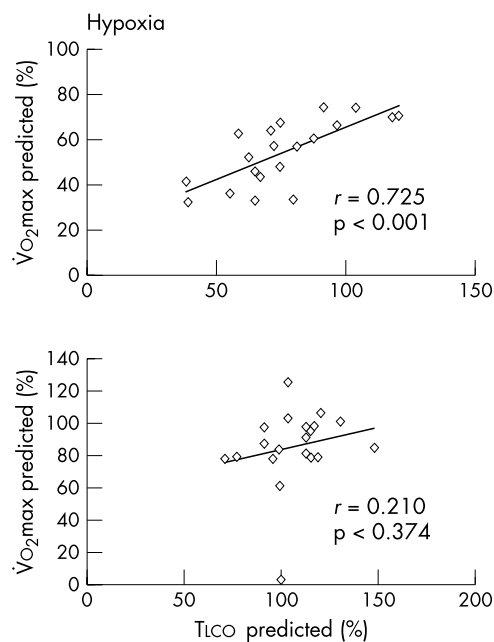
Figure 2 Peak $\dot{V}O_2$ during hypoxia v resting lung transfer capacity for carbon monoxide (T_{LCO}) (both reported as per cent of predicted) in heart failure patients (upper panel, n = 20) and healthy subjects (lower panel, n = 20) (group A). In chronic heart failure, the correlation between T_{LCO} and peak $\dot{V}O_2$ increased further during hypoxia.

confounding by variables such as age, sex, or anthropometric measurements, both resting T_{LCO} and peak $\dot{V}O_2$ are reported as per cent of predicted normal values.

Exercise capacity in hypoxic condition (group A)

With normoxia, peak exercise $\dot{V}O_2$ was 1285 (395) and 1861 (563) ml/min in patients and controls, respectively. The maximum work rate achieved was 101 (36) W in the patients and 163 (54) W in the controls. With hypoxia ($FiO_2 = 16\%$), peak $\dot{V}O_2$ reduced to 1081 (396) in patients and to 1771 (457) and in normal subjects, respectively ($p < 0.01$ and $p < 0.05$ v normoxic condition); the maximum work rate was reduced to 87 (34) W in patients and to 157 (52) W in normal subjects ($p < 0.01$ and $p < 0.05$ v normoxic condition). With hypoxia, in both patients and normal subjects ventilation was increased at rest and throughout the test compared with normoxic levels, but not at peak exercise (table 2). Resting T_{LCO} was correlated with peak $\dot{V}O_2$ obtained under hypoxic conditions (fig 2), with an R value greater than in normoxic conditions (0.725 and 0.619, respectively). Resting T_{LCO}, D_M, and V_C did not predict the reduction in exercise capacity with hypoxia, either in patients or in controls.

T_{LCO} during exercise

T_{LCO} increased during exercise at low work rates (20% of maximum workload) in both normal subjects and heart failure patients (fig 3, data from group A). This increase reflected the increase in V_C and D_M (table 3, data from group B). The patients with the greater capacity to increase T_{LCO} during submaximal exercise were those who showed a smaller reduction in exercise capacity with hypoxia (fig 4, data from group A).

Blood gas values and exercise capacity in normoxic and hypoxic conditions

Haemoglobin concentration, PO_2, SaO_2, CaO_2, alveolar pO_2, and $\Delta P[A-aO_2]$ at rest and peak exercise in normoxic and hypoxic conditions are reported in table 4; each datum is the mean of three measurements. In the normoxic condition PO_2, CaO_2, alveolar PO_2, and $\Delta P[A-aO_2]$ increased during exercise in both patients and normal controls. With hypoxia the resting data were comparable between the normal subjects and the patients. At peak exercise, PO_2 and SaO_2 decreased compared with resting values in both patients and normal controls.

Table 2 Ventilation, tidal volume, and respiratory rate at rest and on peak exercise under normoxic and hypoxic conditions in patients with heart failure (n = 20) and normal controls (n = 20) (group A)

	Normoxia		Hypoxia	
	Rest	Peak exercise	Rest	Peak exercise
Heart failure patients				
Ventilation (l/min)	11 (2)	58 (18)*	28 (6)†	57 (19)*
Tidal volume (l)	0.6 (0.1)	1.6 (0.4)*	1.3 (0.2)*†	1.6 (0.4)*
Respiratory rate (beats/min)	19 (4)*	37 (7)	21 (4)*	36 (7)
Normal controls				
Ventilation (l/min)	10 (2)	69 (19)	28 (5)†	72 (18)
Tidal volume (l)	0.6 (0.1)	2.1 (0.6)	1.5 (0.3)†	2.3 (0.6)
Respiratory rate (beats/min)	15 (4)	34 (5)	18 (3)	32 (8)

Data are presented as mean (SD).
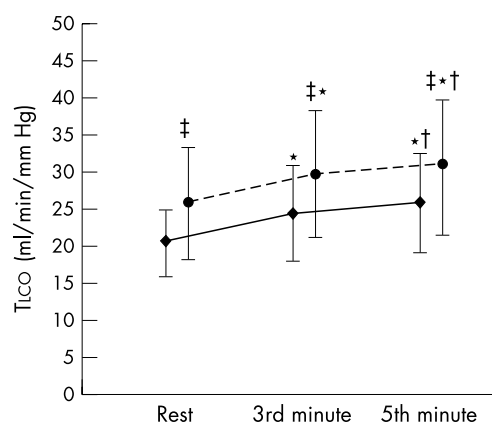*p < 0.01 v normal controls; †p < 0.01 v normoxia.

Figure 3 Lung transfer capacity for carbon monoxide (T_{LCO}) at rest (on the bicycle ergometer) and at the third and fifth minute of constant workload exercise (20% of peak exercise workload). Circles, normal subjects; diamonds, chronic heart failure patients. *p < 0.01 v rest; †p < 0.01 v 3rd minute value; ‡p < 0.01 v chronic heart failure patients.
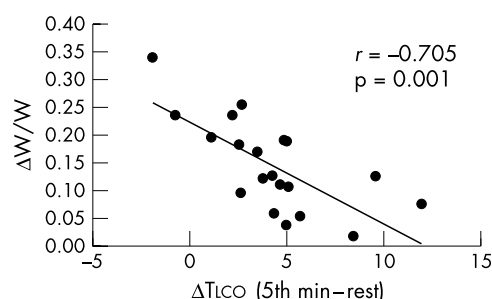

Figure 4 Reduction of exercise capacity with hypoxia. $\Delta W/W$ = [maximum workload achieved in normoxia – maximum workload achieved in hypoxia]/maximum workload achieved in normoxia. ΔT_{LCO} = differences in lung diffusing capacity for carbon monoxide between the fifth minute of exercise and rest in heart failure patients. Patients with the greatest capability to increase T_{LCO} during exercise are those who show the smallest reduction in exercise capacity in hypoxia.

In group A patients there was a weak but significant correlation between resting T_{LCO} and (1) Sao_2, (2) Cao_2, and (3) arterial Po_2 at rest and at peak exercise, in both normoxic and hypoxic conditions; resting T_{LCO} was also weakly correlated with haemoglobin at peak exercise during both normoxia and hypoxia (table 5). In contrast to the patients, in normal subjects resting T_{LCO} was significantly correlated only with haemoglobin and Cao_2, measured during normoxia and hypoxia both at rest and at peak exercise. None of the heart failure patients showed significant (> 3%) haemoglobin desaturation either at rest or peak exercise in normoxic conditions (mean Sao_2 at rest 97.2 (0.8)%, range 94.7–98.4%; mean Sao_2 at peak exercise 97.5 (1.4)%, range 93.2–99.0%). Correlations between peak $\dot{V}o_2$ and Sao_2, haemoglobin, Cao_2, and Po_2

in both patients and normal controls are reported in table 6. The correlations between peak $\dot{V}o_2$ and Cao_2 and haemoglobin were significant in patients and controls in all the conditions studied.

The $\Delta P[A{-}ao_2]$ value in the patients was greater at rest with normoxia than in the normal controls (table 4). However, the increase at peak exercise was greater in the controls than in the patients (14.4 (6.4) v 5.8 (10.0) mm Hg, p < 0.01). With hypoxia the increase in the $\Delta P[A{-}ao_2]$ value from rest to peak was 11.9 (5.9) mm Hg and 15.9 (9.1) mm Hg in patients and in normal subjects, respectively (NS). There was a significant correlation between resting T_{LCO} and $\Delta P[A{-}ao_2]$ at peak exercise in normoxia and at rest and peak exercise in hypoxia in patients but not in normal subjects (table 7). Adjusting $\Delta P[A{-}ao_2]$ for peak $\dot{V}o_2$ strengthened this correlation at peak exercise in the patients, and made it evident in the normal subjects (table 7). Best fit analysis showed that a curvilinear relation significantly improved the correlation of $\Delta P[A{-}ao_2]$, adjusted for peak $\dot{V}o_2$, with T_{LCO} in both normoxic (fig 5, upper panel) and hypoxic conditions (fig 5, lower panel).

DISCUSSION

This study contains several observations aimed at elucidating the complex interplay between lung diffusion abnormalities and impairment of exercise capacity in patients with heart failure.

In the first place, our study confirms that in patients with heart failure, resting T_{LCO} correlates with peak $\dot{V}o_2$. Although we were only able to show a correlation and not a cause–effect link, we believe that a causal relation between impaired T_{LCO} and reduced exercise capacity exists; indeed when the physiological impact of T_{LCO} reduction is increased, as with hypoxia, the correlation between T_{LCO} and peak $\dot{V}o_2$ is high.

Second, our study provides evidence that in heart failure patients, even though resting and peak exercise Sao_2, Po_2, and Cao_2 are in the normal range, their values correlate with T_{LCO}, that T_{LCO} increases during exercise as a result of increases in both V_C and D_M, and that patients who have the greatest capability to increase their T_{LCO} during exercise are those who have the smallest reduction in exercise capacity with hypoxia.

Finally, in both normoxic and hypoxic conditions, the value of the $\Delta P[A{-}ao_2]$ differences is related to T_{LCO}, so when oxygen flow across the alveolar capillary membrane has to increase, as with exercise, or is impaired, as in hypoxia, the $\Delta P[A{-}ao_2]$ difference increases more the lower the resting T_{LCO} value.

The patients we studied belong to a cohort of subjects regularly followed in our heart failure clinic. They were in stable clinical condition and, as in several previous reports,[2–5 20 21] results of standard pulmonary function tests and T_{LCO} showed mild restrictive lung disease and impairment of diffusion. As previously reported,[2 3] T_{LCO} impairment at rest correlates with exercise capacity. However, even if several pieces of evidence suggest a link between T_{LCO} and exercise capacity, the physiological meaning of this correlation remains controversial because, in contrast with patients with pulmonary disease,

Table 3 CO transfer (T_{LCO}) subcomponents during submaximal exercise (group A, 20 heart failure patients and 20 normal controls)

	Heart failure subjects		Normal controls	
	Rest	5th minute	Rest	5th minute
D_M (ml/min/mm Hg)	29.1 (8.4)*	36.4 (12.8)*†	46.9 (14.0)	51.3 (19.2)†
D_M/Va	5.4 (1.3)*	6.6 (2.5)*†	8.0 (2.1)	8.7 (2.5)†
V_C (ml)	109 (42)	145 (65)*†	104 (39)	134 (31)†

Data are presented as mean (SD).
*p < 0.01 v normal controls; †p < 0.01 v values at rest.
D_M, molecular diffusion for carbon monoxide across the alveolar–capillary membrane; D_M/Va, D_M normalised for alveolar volume; V_C, pulmonary capillary blood volume.

Table 4 Haemoglobin concentration, P_{O_2}, S_{aO_2}, C_{aO_2}, and P_{aCO_2} at rest and during peak exercise under normoxic and hypoxic conditions (group A, 20 heart failure patients and 20 normal controls)

	Normoxia		Hypoxia	
	Rest	Peak exercise	Rest	Peak exercise
Heart failure patients				
Hb (g/dl)	14.0 (1.5)	14.9 (1.6)*	14.3 (1.4)	15.0 (1.4)*
P_{O_2} (mm Hg)	86 (6)	99 (11)*	68 (9)†	61 (8)*†
S_{aO_2} (%)	97.2 (0.8)	97.7 (1.2)	94.9 (2.0)†	92.1 (3.1)*†
C_{aO_2} (ml/100 ml)	18.3 (2.0)	19.5 (2.2)*	18.1 (1.9)	18.5 (2.3)*†
pH	7.42 (0.03)	7.40 (0.04)*	7.46 (0.05)	7.44 (0.04)*
P_{AO_2} (mm Hg)	100 (8)	119 (5)*	79 (4)†	84 (4)*†
$\Delta P[A-aO_2]$ (mm Hg)	14.7 (7.6)	20.5 (10.0)*	11.1 (8.8)†	23.0 (7.8)*
P_{aCO_2} (mm Hg)	36.8 (4.5)	33.3 (5.5)*	31.2 (4.1)†	32.1 (4.4)
Normal controls				
Hb (g/dl)	14.1 (1.4)	15.1 (1.4)*	14.2 (1.5)	15.2 (1.3)*
P_{O_2} (mm Hg)	92.9 (6.0)	98.5 (7.0)*	74.6 (9.5)†	67.6 (7.2)*†
S_{aO_2} (%)	97.8 (0.6)	97.8 (0.5)	96.2 (1.6)†	93.8 (2.2)*†
C_{aO_2} (ml/100 ml)	18.5 (1.9)	19.8 (1.8)*	18.3 (1.8)	19.1 (1.7)*†
pH	7.42 (0.02)	7.37 (0.04)*	7.46 (0.04)†	7.39 (0.04)*†
P_{AO_2} (mm Hg)	97.0 (4.8)	117.2 (4.5)*	77.4 (6.8)†	88.1 (5.4)*†
$\Delta P[A-aO_2]$ (mm Hg)	4.2 (6.5)	18.6 (5.6)*	3.0 (5.3)	20.4 (4.9)*
P_{aCO_2} (mm Hg)	36.9 (3.3)	33.9 (3.8)*	30.6 (4.2)†	30.5 (4.0)†

Values are presented as mean (SD).
*p < 0.05 v rest; †p < 0.05 v normoxia.
C_{aO_2}, arterial oxygen content; $\Delta P[A-aO_2]$, alveolar–arterial pressure difference for oxygen; Hb, haemoglobin; P_{aCO_2}, arterial carbon dioxide tension; P_{AO_2}, alveolar oxygen pressure; P_{O_2}, arterial oxygen tension; S_{aO_2}, haemoglobin saturation with oxygen.

Table 5 Correlations between resting carbon monoxide transfer (T_{LCO}) and haemoglobin oxygen saturation, arterial oxygen content, haemoglobin, and arterial oxygen tension (group A, 20 heart failure patients and 20 normal controls)

	S_{aO_2}	C_{aO_2}	Hb	P_{O_2}
Heart failure patients				
Normoxia, rest	R=0.633, p<0.01	R=0.438, p=0.06	R=0.394, NS	R=0.674, p<0.01
Normoxia, peak exercise	R=0.503, p<0.02	R=0.499, p<0.03	R=0.483, p<0.05	R=0.488, p<0.02
Hypoxia, rest	R=0.479, p<0.03	R=0.503, p<0.03	R=0.425, NS	R=0.417, p=0.06
Hypoxia, peak exercise	R=0.541, p<0.01	R=0.500, p<0.03	R=0.476, p<0.03	R=0.541, p<0.01
Normal controls				
Normoxia, rest	R=−0.140, NS	R=0.645, p<0.01	R=0.655, p<0.01	R=−0.148, NS
Normoxia, peak exercise	R=−0.216, NS	R=0.688, p<0.01	R=0.690, p<0.01	R=0.164, NS
Hypoxia, rest	R=−0.210, NS	R=0.678, p<0.01	R=0.684, p<0.01	R=−0.192, NS
Hypoxia, peak exercise	R=−0.087, NS	R=0.563, p<0.01	R=0.603, p<0.01	R=−0.148, NS

Data were obtained from means of three samples.
C_{aO_2}, arterial oxygen content; Hb, haemoglobin; P_{O_2}, arterial oxygen tension; S_{aO_2}, haemoglobin saturation with oxygen.

exercise induced haemoglobin desaturation is rare in patients with heart failure. A cardiopulmonary exercise test with a reduced O_2 fraction is a safe test used to assess exercise capacity at moderate altitude.[22] With hypoxia, peak $\dot{V}_{O_2}$ and maximum work rate were reduced in both heart failure patients and normal controls. It is noteworthy that the correlation between T_{LCO} and exercise capacity was high in the hypoxic tests (fig 2), a condition where T_{LCO} impairment is likely to became more important.

In normal subjects we found a correlation between T_{LCO} and C_{aO_2}, probably mediated by haemoglobin. In heart failure patients, in contrast, resting T_{LCO} correlated with arterial S_{aO_2}, P_{O_2}, and C_{aO_2} both at rest and during peak exercise in normoxic conditions; this suggests that in patients who are not able to increase their cardiac output adequately during exercise, the C_{aO_2} at rest and its increase during exercise[11 23] became relevant determinants of oxygen delivery (and therefore of exercise capacity) (table 3). Accordingly, even if the S_{aO_2}, arterial P_{O_2}, and C_{aO_2} values which we measured in the normoxic condition are within the so called "normal range"

(table 4),[24] values at the lower end of this range are functionally relevant. In other words, it makes a difference for a heart failure patient whether they have a haemoglobin of 12 mg/dl or 15 mg/dl, or an S_{aO_2} of 94% or 98%. Furthermore, our data confirm the role of an increase in haemoglobin as a determinant of exercise capacity.[11]

To our knowledge, blood gas analyses during exercise in hypoxia have not previously been reported in patients with heart failure. In normal subjects as well as in heart failure patients, resting T_{LCO} was significantly correlated with haemoglobin and C_{aO_2}, measured at peak exercise, suggesting that in hypoxia C_{aO_2} becomes a relevant determinant of exercise capacity. The observed reduction of P_{O_2} and S_{aO_2} is counterbalanced by an increase in haemoglobin concentration,[25] which serves to obviate an undesirable reduction of C_{aO_2} during exercise. Two explanations for the decrease in arterial P_{O_2} at peak exercise with hypoxia are likely. In the first place, there could be a hypoxia induced increase in pulmonary shunting because of hypoxic pulmonary vasoconstriction enhancing the ventilation–perfusion mismatch; secondly, the pulmonary

Table 6 Correlations of peak oxygen consumption with haemoglobin saturation with oxygen, arterial oxygen content, haemoglobin, and arterial oxygen tension (group A, 20 heart failure patients and 20 normal controls)

	Sao_2	Cao_2	Hb	Po_2
Heart failure patients				
Normoxia, rest	R=0.515, p<0.02	R=0.509, p<0.02	R=0.474, p<0.05	R=0.569; p<0.01
Normoxia, peak exercise	R=0.333, NS	R=0.557, p<0.01	R=0.561, p<0.01	R=0.340, NS
Hypoxia, rest	R=0.243, NS	R=0.478, p<0.04	R=0.462, p=0.05	R=0.187, NS
Hypoxia, peak exercise	R=0.462, p<0.04	R=0.542, p<0.01	R=0.538, p<0.02	R=0.525, p<0.02
Normal controls				
Normoxia, rest	R=0.315, NS	R=0.597, p<0.01	R=0.615, p=0.01	R=−0.003, NS
Normoxia, peak exercise	R=0.143, NS	R=0.674, p<0.01	R=0.696, p<0.01	R=−0.434, NS
Hypoxia, rest	R=−0.306, NS	R=0.539, p<0.02	R=0.662, p<0.02	R=−0.315, NS
Hypoxia, peak exercise	R=−0.291, NS	R=0.532, p<0.02	R=0.677, p<0.01	R=−0.231, NS

Data were obtained from means of three samples.
Cao_2, arterial oxygen content; Hb, haemoglobin; Po_2, arterial oxygen tension; Sao_2, haemoglobin saturation with oxygen.

Table 7 Correlation between resting carbon monoxide transfer ($Tlco$) and alveolar–arterial pressure difference for oxygen (group A, 20 heart failure patients and 20 normal controls)

	Heart failure patients	Normal controls
$\Delta P[A-ao_2]$, normoxia, rest	R=−0.439, p=0.06	R=0.06, NS
$\Delta P[A-ao_2]$), normoxia, peak exercise	R=−0.516, p<0.02	R=−0.211, NS
$\Delta P[A-ao_2]$, hypoxia, rest	R=−0.502, p<0.02	R=−0.106, NS
$\Delta P[A-ao_2]$, hypoxia, peak exercise	R=−0.625, p<0.01	R=−0.207, NS
$\Delta P[A-ao_2]/\dot{V}o_2$, normoxia, rest	R=−0.384, NS	R=−0.022, NS
$\Delta P[A-ao_2]/\dot{V}o_2$, normoxia, peak exercise	R=−0.720, p<0.01	R=−0.488, NS
$\Delta P[A-ao_2]/\dot{V}o_2$, hypoxia, rest	R=−0.431, p=0.06	R=0.049, NS
$\Delta P[A-ao_2]/\dot{V}o_2$, hypoxia, peak exercise	R=−0.794, p<0.01	R=−0.791, p<0.01

$\Delta P[A-ao_2]$, alveolar–arterial pressure difference for oxygen; $\dot{V}o_2$, oxygen uptake.
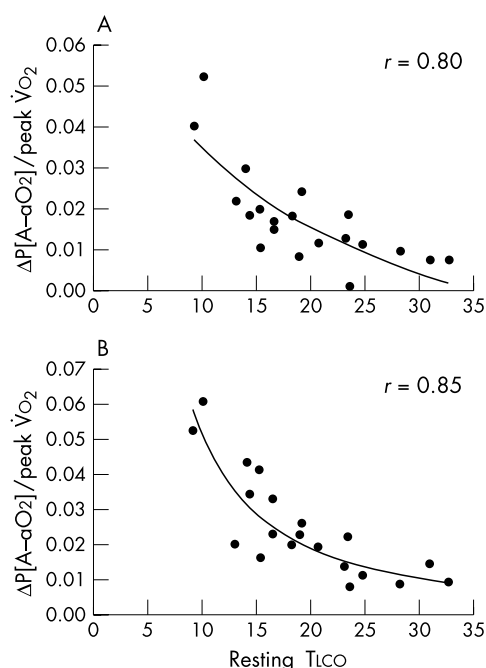
capillary transit time could be too short for a reduced alveolar Po_2 to achieve an equilibrium between alveolar and capillary Po_2 pressures. Indeed with hypoxia the $A-ao_2$ gradient increased compared with normoxia, both at rest and during peak exercise (table 6). An inadequate exercise induced increase in ventilation during hypoxia is unlikely because $Paco_2$ levels did not increase.

Smith and colleagues[3] recently showed that $Tlco$ increases during light exercise in heart failure patients.[3] Our findings are consistent with that report and provide new information about the cause of the exercise induced increase in $Tlco$. $Tlco$ depends on membrane diffusion capacity and capillary volume, and both were increased during exercise in our heart failure patients and normal controls. The increase in Vc is likely to be caused by pulmonary vessel recruitment. The exercise induced increase in Dm is more difficult to understand. The increase in Dm during exercise confirms that Dm is not a fixed value but can increase. This observation is in line with the suggestion that $Tlco$ should be used as an antifailure treatment target.[3 4] It is not possible to measure $Tlco$ or its components reliably at peak exercise when haemoconcentration can further increase $Tlco$ by increasing the surface of the alveoli in contact with the red blood cells.[25] We measured $Tlco$ during light exercise (around 20% of the maximum workload achieved) and therefore we cannot say whether this value represents the maximum possible increase in $Tlco$ or not. We used a light workload to show that $Tlco$ can be increased and that at the same increment of work rate the increase in $Tlco$ correlates with the capacity of the subjects to adjust to exercise under hypoxic conditions. Indeed we showed that patients who increase $Tlco$ most during exercise are those with the least reduction in hypoxia induced exercise capacity—meaning that the increase in $Tlco$ during exercise can be viewed as a compensatory mechanism.

Figure 5 Correlation between alveolar–arterial O_2 differences at peak exercise divided by peak $\dot{V}o_2$ ($\Delta P[A-ao_2]/$ peak $\dot{V}o_2$) *v* resting diffusing capacity for carbon monoxide ($Tlco$) in normoxia (upper panel) and hypoxia (lower panel).

Conclusions
While none of the present evidence, when considered in isolation, proves a causal role of $Tlco$ impairment in the reduced

exercise capacity of patients with heart failure, collectively the following findings strongly suggest that its role is indeed causal:

- the resting T_{LCO} correlates with exercise capacity and that this correlation is increased with hypoxia

- a low but "normal" arterial haemoglobin content, Sao_2, and Cao_2 are associated with reduced exercise performance in heart failure patients

- a reduced capacity to increase T_{LCO} during submaximal effort correlates with the reduction of exercise capacity with hypoxia

- if resting T_{LCO} is low at peak exercise with hypoxia, then the $\Delta P[A-ao_2]$ difference shows the greatest oxygen gradient.

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Authors' affiliations
P G Agostoni, M Bussotti, P Palermo, M Guazzi, Centro Cardiologico Monzino, IRCCS, Institute of Cardiology, University of Milan, Milan, Italy

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IMAGES IN CARDIOLOGY ....

Subaortic stenosis caused by two discrete membranes

A 15 year old girl presented with fatigue and dyspnoea on exertion. She had an ejection murmur at the left sternal border. A chest radiograph showed cardiomegaly and the ECG showed left ventricular hypertrophy with a strain pattern. The echocardiogram confirmed left ventricular hypertrophy, with outflow obstruction caused by subaortic stenosis at two separate levels, one immediately proximal to the aortic valve appearing as a fibrous ridge (upward arrow) and the other as a discrete membrane. Cardiac catheterisation confirmed two discrete intracavitary pressure gradients. Subaortic stenosis is usually caused by a discrete membrane or fibromuscular ridge and may very rarely be due to a fibrous tunnel involving the whole left ventricular outflow tract. Obstruction caused by two separate but very discrete membranes as occurred in our patient also appears to be very rare. At operation both obstructions were resected and the patient made a good recovery. She will, however, require long term follow up as recurrence of subaortic stenosis after surgical treatment is known to occur in a proportion of cases.

M B Yilmaz
E Akarca
Ú Gűray
cardioceptor@ttnet.net.tr